treatment, said method comprising:

administering to said patient first dosages at least daily for a period of from 7 to 28 days, said first dosages each comprising carvedilol,

then administering to said patient second dosages at least daily for a period of from 7 to 28 days, said second dosages each comprising carvedilol, and

then administering to said patient third dosages daily for a maintenance period, said third dosages each comprising carvedilol, said third dosages each comprising a daily maintenance dose in the range of from about 10 mg to about 100 mg of carvedilol,

said first dosages each comprising carvedilol in an amount which his 10-30% of said daily maintenance dose,

said second dosages each comprising carvedilol in an amount which is 20-70% of said daily maintenance dose.

~~52.~~ 11 Method of claim ~~51~~ 10, wherein carvedilol is administered to the patient once or twice daily.--

Kindly add the attached Abstract as the last page of the specification and claims.

REMARKS

Reconsideration of this application is requested in view of the above new claims and following remarks.

The courtesy of an interview kindly granted by Examiner Phyllis Spivack to counsel and to Prof. Gisbert Sponer, one of the present inventors, on October 5, 1998, is acknowledged with appreciation. It is believed that the presentation of the new claims herein will result in the allowance of the present application.

Certain proposed claims A, B, C and D were discussed with the Examiner, and a copy was left with the Examiner. Claim 42 corresponds to draft claim A, with typographical errors corrected at lines 6 and 10. Claims 48 and 49 are the same as draft claims B and D. Claim 50 is the same as draft claim C, with a typographical error corrected at line 1 thereof. Claim 51 was not discussed during the interview, but is a modification of draft claim A aimed at submitting a claim wherein proof of infringement might be easier to produce than for claim 42.

At the start of the interview, Prof. Sponer described the background to the present invention.

Congestive heart failure (CHF) is a disease which is characterized by impaired function of heart with the consequence that distinct organs are lacking of sufficient blood supply. CHF is not only a disease which markedly disables the patients, but also life expectancy is highly decreased. For example, only 50% of CHF patients with a late state (NYHA IV) survive about 1 year, in mild forms (NYHA II-III) only 50% of the patients survive about 5 years. Therefore, in principle, thegoal of any treatment of CHF patients should be targeted to improve the symptoms (e.g. exercise capacity) and to reduce mortality.

For the treatment of CHF, digitalis glycosides, (loop-) diuretics and vasodilators have been used over a number of decades. Digitalis glycosides increase the myocardial contractility, improve hemodynamic variables and improve symptoms, but digitalis glycosides do not increase live expectancy as confirmed recently in the large epidemiological DIG-trial on about 7800 patients. Diuretics off load the heart by reducing the circulating blood volume and, therefore, symptoms, in particular congestion, can be

reduced by diuretics. There is no study available which shows that diuretics are able to reduce the mortality of CHF patients. It is believed that this topic has never been studied. Also vasodilators can reduce the myocardial pre- and after load and therefore, they can improve the symptoms. Among the different vasodilators, there are inconsistent data available with respect to reduction in mortality. Whereas α_1-adrenoceptor blockers have not been shown to reduce mortality, the combination of hydralazine + isosorbid-dinitrate have been shown to improve the life expectancy to a very small extent (Cohn et al. N. Engl. J. Med. 314; 1547-1552, 1996).

Phospho-diesterase inhibitors (e.g. milrinone) induced very nice hemodynamic effects and improve exercise capacity, but they induce excess mortality (Di Bianco et al. N. Engl J Med. 320; No. 11, p. 677-683, 1989).

On the other hand, in a variety of studies, ACE inhibitors have consistently demonstrated to be effective not only in improving symptoms but also in a prolongation of live expectancy. In summary, there is no correlation between improvement of hemodynamic variables or relief of symptoms and reduction in mortality of patients treated with various drugs. Thus, the goal, to treat the patients for feeling better and living longer was an unmet wish in the past due to the fact that life expectancy could mostly not be improved by compounds being used.

In general, ß-blockers are contra-indicated for patients in CHF due to their negative inotropic effect. However, some studies have been performed in the last 15 years showing that under certain circumstances ß-blockers are able to reduce the symptoms in some patients. Two large mortality trials had been performed with metoprolol and bisoprolol.

Whereas, metoprolol, (MDC-trial, Waagstein et al., Lancet 342: 1441-1446, 1993) examined in patients with dilated cardiomyopathy did not show reduction in mortality, the results of a study with bisoprolol (CIBIS trial, Circulation 99; p 1765-1773, 1994) showed inconsistent results. Whereas the larger group of patients suffering from ischemic heart failure, had no benefit with respect to mortality, a small subgroup of patients with dilated cardiomyopathy had some positive effects.

Carvedilol was investigated in an earlier study in a few patients with CHF. The pilot trial was the investigation published by Das Gupta. In this small trial only hemodynamics and exercise capacity were evaluated. Bearing in mind, that there is no correlation between effects on hemodynamics/exercise capacity and effect on mortality, the next larger trials (US trial forming the basis of this and companion appliaitons) did not give any idea for the expectation of positive results in mortality during the planning phase. This can be documented by the fact that the primary endpoint of this large US programme was exercise capacity, whereas mortality was not a pre-specified efficacy parameter. Mortality was only monitored by a drug safety monitoring board (DSMB), which was independent from the investigators and the sponsor of the study. This DSMB was installed in the study programme since a lot of previous studies with various investigational drugs have shown that improvement of symptoms and hemodynamics were associated with increase (!) in mortality. Therefore, this board was installed to stop the study in case the risk of survival was inferior in comparison to the placebo-controlled patients. It should be noted that in the U.S. programme all the patients received as basal medication the triple combination consisting of digitalis glycosides, diuretics and ACE-inhibitors. One group of the patients

received then additionally carvedilol, the other group additionally only placebo. On the recommendations of the DSMB, the study programme was stopped prematurely due to ethical reason because patients treated with placebo had shown a clear-cut higher mortality rate during the course of the study than the carvedilol treated patients. It should be noted that this effect must be regarded as additional to that obtained with ACE-inhibitors because all patients received ACE-inhibitors as basal medication.

The basic idea of decreasing mortality caused by congestive heart failure in patients is the subject matter of claims which appear in the companion U.S. patent 5,760,069. This patent issued from one of the parent applications of the present case, and the claims of that '069 patent were exhibited to the Examiner during the interview.

The present claims are directed at a different inventive concept than set forth in the claims of the '069 patent. It has been discovered that an unusually low dose level titration method must be used with the CHF patients treated with carvedilol, with the beginning titration dose being, for example, only 10 to 30% of the ultimate daily maintenance dose. This feature of using low amounts of carvedilol in the titration is clearly set forth in the claims herein, and is not taught by the references of record.

In particular, all claims formerly in the application were rejected as unpatentable over the McTavish et al article. McTavish teaches nothing about titrating a patient with unusually low levels of carvedilol, and there is not reason to lead one of only ordinary skill in the art to such a method. In view of this, the 35 USC §103(a) rejection should be withdrawn.

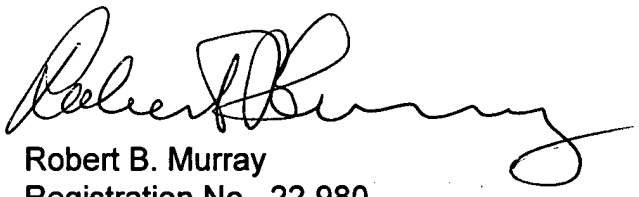
The Examiner required the submission of an Abstract on a separate sheet, and an

appropriate Abstract is attached.

A sincere effort has been made to place the present claims in allowable condition. Should the Examiner feel that the present application could be advanced by a personal discussion with counsel, she is invited to call the undersigned at the number set forth below.

In the event any fees are required, please charge our Deposit Account No. 14-1060.

Respectfully submitted,
NIKAIDO, MARMELSTEIN, MURRAY & ORAM LLP



Robert B. Murray
Registration No. 22,980

Atty. Docket No. P1614-7038
Metropolitan Square
Suite 330 - G Street Lobby
655 15th Street, N.W.
Washington, D.C. 20005-5701

Telephone: (202) 638-5000

RBM/cb